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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/257,650	02/25/99	FUJINO	

EXAMINER	
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ART UNIT	PAPER NUMBER
1646	18

HM12/0621
DIKE, BRONSTEIN, ROBERTS & CUSHMAN
130 WATER STREET
BOSTON MA 02109

DATE MAILED: 06/21/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 4/5/01

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-14, 16-19, 21-24, 26 is/are pending in the application.
Of the above, claim(s) 1-13 is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 14, 16-19, 21-24, 26 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☒ Claim(s) 1-14, 16-19, 21-24, 26 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/

Part III: Detailed Office Action

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 16-19, 21-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 16, 17, and 24 are all incomplete method claims. To be complete, a method claim must state a goal in the preamble of the claim, and conclude having achieved that goal. To use claim 14 as an example, the claim states the goal to be "screening substances for a substance capable of causing an aberrant receptor... to operate in a manner similar to a non-aberrant receptor", however the claim merely concludes with "assaying the operation activity of said substance on said receptor", which does not achieve the stated goal.

Claims 19 and 23 are indefinite because it is not clear how the additional method steps recited therein relate to the method steps of the claims from which they depend, which claims do not reequqire any genes.

Claim 22 is indefinite because it is not clear how a cell "expresses *with* a gene".

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 16-19, 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al., Molecular Endocrinology 8(7):886-894, 1994.

Birnbaumer et al. disclose a mutation in the extracellular (ligand binding) region of type-2 vasopressin receptor to be responsible for X-linked congenital nephrogenic diabetes insipidus (abstract). It was further shown that AVP, arginine vasopressin, the natural ligand, stimulated the mutant receptor with an EC_{50} that was increased over wild-type by about 60-fold (abstract), meeting the limitation of having screened for a substance that would operate the receptor in a manner similar to the wild-type receptor. The affinity for AVP was lower in the mutated receptor than wild type (page 887, second column), by 20-fold (page 889, first col.). Assays were performed on cell lysates, see page 893.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Green et al., J. Biol. Chem. 268(31):23116-23121, 11/5/93.

Green et al. disclose a human β_2-adrenergic receptor with lowered binding affinity for epinephrine as compared to wild type. They screened for, but were not able to find, substances that would operate the receptor in a similar manner to the non-aberrant receptor, see sentence bridging pages 23120-23121.

Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Kong et al., J. Biol. Chem. 268(31):23055-23058, 1993.

Kong et al. disclose a mutated δ opioid receptor with reduced affinity for selective agonists such as enkephalin. They performed assays consistent with claim 14, see Fig. 2 and Table I, and determined that non-selective agonists were able to "operate" the receptor in a manner "similar to non-aberrant receptor."

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 16-19, 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., J. Biol. Chem. 268(15):11272-11277, 5/25/93, previously of record, in view of Choong et al., J. Clin. Endocrinol. Metab. 81(1):236-243, 1996.

Lebrun et al. disclose a naturally occurring mutation in the insulin receptor (aberrant gene product) isolated from two sisters, which causes the disease of extreme insulin resistance. This receptor mutation impairs the ability of the hormone to activate autophosphorylation of receptors and phosphorylation of substrates (operation activity). Lebrun et al. teach a method of screening for monoclonal antibodies (substance or drug) that restores activity (operation activity) to the mutant receptor by assaying the activity of the receptor. An activity assayed was phosphorylation of substrate (signal transduction system), the screen was performed in NIH 3T3 fibroblasts transfected with the gene encoding and expressing either the wild-type or mutant receptors, assays were performed on purified receptors (separating the aberrant gene product), and the activity of the mutant receptor was compared to that of the wild-type receptor. Two monoclonal antibodies were found to activate the mutant receptor kinase.

Lebrun differs from the claims in that the receptor mutation was not in the extracellular, ligand binding portion of the receptor, and that no pharmaceutical composition was prepared.

Choong et al. teach a disease in which partial androgen insensitivity was shown to be due to a mutation in the ligand-binding domain of the androgen receptor (AR) gene. The gene containing the mutation was obtained by recreating the mutation via site directed mutagenesis, expressed in COS cells, and found to have a reduced binding affinity for mibolerone compared with normal AR (see abstract).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the mutated AR of Choong et al. in the method of Lebrun et al. for the purpose of finding an antibody that would compensate for the AR mutation described by Choong et al. One of ordinary skill in the art would have been motivated to do so by the combined teachings of Lebrun et al., who teach that antibodies may be used to induce the conformational changes normally imparted to a receptor by the ligand, including in the case of some mutated receptors, taken with Choong et al., who teach that the single mutation in the ligand binding domain of the AR is responsible for the lowered binding affinity to ligand. Accordingly, the invention is *prima facie* obvious over the cited prior art.

Advisory Information:

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Eileen O'Hara, whose telephone number is (703) 308-3312. Dr. O'Hara can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. **Please** advise the Examiner at the telephone number above when an informal fax is being transmitted.

Lorraine Spector, Ph.D.
Primary Examiner

LMS
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6/20/01